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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,857	08/31/2001	Jei-Fu Shaw	08919-066001 / 09A-900517	2196

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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,857	SHAW ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *33-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/31/01, 10/1/02 &* 5/5/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The application has been amended as requested in the communication filed July 1, 2004. Accordingly, claims 3, 5, 6, 9, 11, 12, 15, 17, 18, 25, 28, and 30-32 have been amended.

Applicant's election without traverse of Group II, claims 1-32 in the reply filed on July 1, 2004 is acknowledged.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see page 4, line 6. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The use of the trademarks GENE PULDER and HIPREP have been noted in this application, see page 17, lines 2, 9, and 13. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

The disclosure is objected to because the amino acid sequences on pages 5-12 are not aligned properly with the nucleic acid sequences to indicate the codon for each amino acid residue as intended by applicant. The black background indicating that a codon has been mutated does not allow the identification of the codon itself. Appropriate corrections are required.

The disclosure is objected to under 37 CFR 1.71, as being so incomprehensible as to preclude a reasonable search of the prior art by the examiner for claims 25 and 32. The nucleic acid sequence of SEQ ID NO: 3 on pages 6 and 7 encoding lipase 3 of SEQ ID NO: 4 contains 1620 nucleotide, whereas that in the sequence listing contains only 1532 nucleotides. SEQ ID NO: 3 in the sequence listing does not encode the polypeptide of SEQ ID NO: 4. Thus, the examiner could not search claims 25 and 32 to determine their patentability.

Applicant is required to submit an amendment, which clarifies the disclosure so that the examiner may make a proper comparison of the invention with the prior art.

Applicant should be careful not to introduce any new matter into the disclosure (i.e., matter which is not supported by the disclosure as originally filed).

Claims 6, 12, 18, and 32 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims

6, 12, 18, and 32 are drawn to a *Candida rugosa* lipase of SEQ ID NO: 4, but SEQ ID NO: 4 is not a wild-type *C. rugosa*, see the specification on page 14, lines 6-8. Thus, claims 6, 12, and 18 improperly dependent directly or indirectly on claim 1, which is limited to the wild-type lipase. Similarly, claim 32 is improperly dependent on claim 26 because claim 26 is limited to the wild-type lipases.

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are reasons for the rejections:

(1) The clause "includes at least 12 codons corresponding to CTG codons in the wild-type DNA, each of the 12 codons, independently, being TCT, TCC, TCA, TCG, AGT, or AGC" in claim 1 renders the claim indefinite and confusing. For examination purposes only, the clause is taken to mean, "Wherein the CTG codon is substituted with a codon selected from the group consisting of TCT, TCC, TCA, TCG, AGT, or AGC."

(2) The clause "wherein the amino acid sequence of the *Candida rugosa* lipase is SEQ ID NO: 4" in claims 6, 12, 18 and 32 renders the claims confusing and indefinite for the reasons set forth in the objection to the claims.

(3) The phrase "correspond to at least CTG codons" in claim 26 renders the claims confusing and indefinite. For examination purposes only, the phrase is taken to mean, "Substitute at least 12 CTG codons".

(4) SEQ ID NO: 3 in the sequence listing (1532 bp), and that in the specification on pages 6 and 7 (1641 bp) do not match which renders the claim indefinite and confusing. Also, SEQ ID NO: 3 of the sequence listing does not encode SEQ ID NO: 4. Thus, claims 25 and 32 are found indefinite and confusing and could not be searched.

(5) Claims 5, 7, 9, 11, 13, 15, 17, 19-24, 30, and 31 are included in this rejection because they are dependent on rejected claims and do not cure their deficiencies.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-11, 13-17, 18-24, and 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bocca *et al.* (IDS reference: Prot. Sci 1998, 7, pp 1415-1422) or WO 99/14338 ('338, IDS reference) in view of Lotti *et al.* (IDS reference: Gene 1993, 124, pp. 45-55), and Ge *et al.* (IDS reference: BioTechniques 1997, 22, 28-29).

Brocca *et al.* teach the heterologus overexpression of *Candida rugosa* lipase 1 (CRL1) in both *Saccharomyces cerevisiae* and *Pichita pastoris* in an active form, see the abstract. They disclose that the CUG codon, a universal codon for leucine, is read as serine, and that 20 out of the 47 serine residue in the LIP1 gene are encoded by CUG including the active site catalytic Ser-209, see page 1415, right column, second paragraph through the end of the first paragraph on page1416. They constructed mutated LIP1 genes by site directed mutagenesis in which 2-8 CUG codon are substituted with universal serine codons, see the paragraph bridging left and right column on page 1416, and Table 1. Also, they constructed a synthetic gene in which all the 19 CTGs codons are substituted with universal serine codons and the substitution of uncommon codons with common codons for *S. cerevisiae* and *P. pastoris*, see the paragraph bridging pages 1416 and 1417. In addition, they teach the construction of a vector comprising said the synthetic gene and the transformation *S. cerevisiae* and *P. pastoris*.

The '388 document teaches the heterologus overexpression of *Candida rugosa* lipase 1 (CRL1) in both *Saccharomyces cerevisiae* and *Pichita pastoris* in an active form, the abstract. It discloses that the CUG codon, a universal codon for leucine, is read as serine, and that 20 out of the 47 serine residue in the LIP1 gene are encoded by CUG including the active site catalytic Ser-209, see page 1415, see from the last paragraph on page 1 through line 23 on page 2. It teaches that five member of *C. rugosa* have been previously cloned and sequenced, and used site directed mutagenesis to obtain mutated LIP1 genes in which 2-8 CUG codon are substituted with universal serine codons, see page 5, lines 20-29. Also reported is the construction of a synthetic gene in which all the 19 CTGs codons are substituted with universal serine codons and the substitution of uncommon codons with common codons for *S. cerevisiae* and *P. pastoris,* see the paragraph bridging pages 1416 and 1417. In addition, they teach the construction of a vector comprising said the synthetic gene and the transformation *S. cerevisiae* and *P. pastoris*.

Lotti *et al.* teach the cloning of three lipases from *Candida cylindracea* which became known later as *C. rugosa*, see the abstract. In Figure 2A, they teach the nucleic acid encoding the lip3 and the corresponding amino acid sequence.

Ge *et al.* teach a method by which simultaneous multisite specific mutations can be introduced by using overlap extension.

Both Brocca *et al.* and the '338 document provide one of ordinary skill in the art to develop a method for making *C. rugosa* lipases in large quantities for industrial purposes as they teach that said lipases are among the commercial lipases most often employed in the hydrolysis and synthesis of wide range of esters for commercial interest, Brocca *et al.*, left column after the abstract, and page 1 lines 8-15 of the '338 document. Also, they provide a motivation for substituting specifically all CTG codons found in the wild-type coding sequence by a serine codon in order to express the lipases in a heterologus host cells such as *E. coli* or Yeast as they teach *C. rugosa* read CTG codon as a serine instead of leucine in almost all other organisms as they teach the synthetic gene in which all CTG codones are substituted with a universal serine codon are expressed to produce enzymatically active lipase, whereas partially substituted eight CTG codons produced inactive and unsecreted protein. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to prepare a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 4 or variant thereof in which all the CTG codons (about 19 in the coding sequence of Lip3) are substituted by any one of the universal serine codons, TCT, TCC, TCA, TCG, AGT, or AGC in the coding sequence of Lip3 taught by Lotti *et al.* by site directed mutagenesis, preferably using the simaltaneous introduction of multiple mutations method taught by Ge *et al.* Alternatively, the ordinary skilled in the art would have used the combined chemical and enzymatic synthesis taught by both Brocca *et al.* and the '338 document to substitute all the CTG codons. It should be noted changing all the CTG codon would produce a nucleic acid, which is > 96% identical to that of the wild type coding sequence (claim 1-5, 7-11, 13-17, and 26-30). Also, it should be noted the ordinary skilled in the art would have replaced few uncommon codons for the host cell at the 5'-end of the coding sequence with common codons, and designed appropriate restriction site(s) to insert the coding sequence into a desired vector by well-known methods in the art. It would have been further obvious to one of ordinary skill in the art to insert the mutant coding sequence into an expression vector and transform a host cell such as *S. cerevisiae* and *P. pastoris* as taught by Brocca *et al.* and the '338 document, and utilizes the transformed host cell in a recombinant method to make the enzymatically active Lip3 (claim 18-24). It should be noted the ordinary skill in the art would have had the skills, the motivation and the knowledge to make the claimed invention. He/she would have had a reasonable expectation of success from the teaching Brocca *et al.* and the '338 document because the prior art teach that the substitution of all CTG codons in the coding sequence of *C. rugosa* lipase 1 led to the heterologus expression of Lip1 in an active form. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

Claims 6, 12, 18, and 31 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1652